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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/320,713	05/27/1999	REINHARD EBNER	PF470	5190

22195 7590 11/30/2001

HUMAN GENOME SCIENCES INC
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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/30/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

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	14

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 9/18/01.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 25, 27, 29, 37-40, 44, 46, 50-155 is/are pending in the application.

Of the above, claim(s) 25, 27, 29, 37-40, 44, 46, 50-73, 76-82, 94, 112, 118-121, 128-155 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 74, 75, 83-90, 113-117, 122-127 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 25, 27, 29, 37-40, 44, 46, 50-155 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 9

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of the sequence of nucleic acids encoding SEQ ID NO:4 residues 28-160 in Paper No. 13, filed 9/18/01 is acknowledged. The traversal is on the ground(s) that (a) the Examiner has not shown that examination of the entire invention would present a serious search burden, (b) that the Examiner has not disclosed any statutory or regulatory basis for requiring the election of an individual sequence within the previously elected Group I, (c) that the current restriction represents a restriction within a Markush group, and that said Markush group has members that are sufficiently few in number and very closely related, so that a search of all members may be made without a serious burden, and (d) that the Examiner has not addressed MPEP 804.03, directed to nucleotide sequences, in which the Commissioner authorized a partial waiver of restriction practice, allowing the examination of up to ten sequences, and further traversing that the instant nucleic acids encode different fragments of the same protein, rather than different proteins. These arguments are not found persuasive because:

With respect to point (a) above, the Examiner explained clearly why the multitude of claimed sequence present a serious search burden in the presentation of the requirement in paper number 10, to whit: the search for more than one product would be burdensome, because each is claimed not by nucleic acid sequence, but by the sequence of the protein encoded thereby, and requires a search of the corresponding region of SEQ ID NO: 3 as well as a 'reverse translation' search of the corresponding region of SEQ ID NO: 4, such that each individual sequence requires two sequence searches which are not required for any of the other sequences. Due to the use of 'comprising' language, it cannot even be said that the search for nucleic acids encoding amino acids 1-160 of SEQ ID NO: 4 would reveal art pertaining to, for instance a nucleic acid *comprising* a region encoding amino acids 19-27 of SEQ ID NO: 4, as the latter could be found embedded in a completely different protein. "

With respect to point (b) above, the statutory basis for this requirement is U.S.C. 121. The Examiner regrets failing to make this clear in the previous Office Action.

With respect to point (c) above, that the current restriction represents a restriction within a Markush group, and that said Markush group has members that are sufficiently few in number and very closely related, so that a search of all members may be made without a serious burden, the Examiner notes MPEP 803.02, which states:

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction.
>
> Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility.

In this case, the first requirement is not met, in that the members of the group are not sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden. Specifically, claim 67 alone encompasses 113,905 patentably distinct nucleic acids, some as short as 3 or 6 nucleotides' in length, which could, due to the use of 'open' language, be found embedded in any number of prior art nucleic acids. With respect to the search burden that this presents, see the discussion of point (a), above.

Further, contrary to the second paragraph quoted from the MPEP above, there is no unity of invention here, as no common utility has been presented, and there is no substantial structural feature disclosed as being essential to that utility; such would seem impossible, as the claimed fragments are, in many cases, non-overlapping, and thus do not share *any* structural feature.

Finally, with respect to applicant's point (d), that the Examiner has not addressed MPEP 804.03, directed to nucleotide sequences, in which the Commissioner authorized a partial waiver of restriction practice, allowing the examination of up to ten sequences, and further traversing that the

instant nucleic acids encode different fragments of the same protein, rather than different proteins. The Examiner notes that the correct MPEP citation is MPEP 803.04, not 804.03. The issue in question was a partial waiver of restriction practice to allow examination of up to ten sequences. This waiver was issued in 1996. Since then, the nucleic acid and protein databases that must be searched for each of the independent and distinct sequence claimed herein have multiplied many fold in size, such that it is now burdensome to search more than a single sequence in an application. Further, the waiver allowed, but did not require the Examiner to search ten sequences. With respect to applicants second point, it is not true that the claimed nucleic acids merely encode different fragments of the same protein, rather than different proteins. As many of the fragments are quite short, and could be embedded within other patentably distinct proteins, it cannot be said that they are merely fragments of a common protein, and a separate search is required for each possible fragment.

The requirement is still deemed proper and is therefore made FINAL.

The elected invention is nucleic acids which encode SEQ ID NO: 4, residues 28-160. Applicants have erroneously identified claim 79 as corresponding to the elected invention. This cannot be the case, as claim 79 is directed to residues 28-160 of SEQ ID NO: 2, not SEQ ID NO: 4. As applicants did not identify deposited strain 209665 as corresponding to the elected invention, it is presumed that it does not. If applicants later identify the deposited strain as corresponding to the elected invention, then a requirement will be made under 35 U.S.C. §112, first paragraph that the terms of deposit be in conformance with the requirements of MPEP 2414.01.

Thus, claims, 74-75, 83-90, 113-117, and 122-127 as they are drawn to the elected invention, are under consideration. Claims 29, 37-40, 44, 46, 50-73, 76-82, 91-112, 118-121 and 128-155 are withdrawn from prosecution as being drawn to a non-elected invention.

11/28/01

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are directed.

Claims 74-75, 83-90, 113-117, and 122-127 are objected to for encompassing multiple patentably distinct inventions. The claims should be amended to include only the elected invention. Correction is required.

The information disclosure statement filed 2/5/01, paper 9, has been considered. References AH-BX are not considered as they are merely sequences with no explanation of relevance or alignment with the disclosed sequences, such that relevancy to the claimed invention cannot be assessed.

It is noted that the specfication refers to the protein of SEQ ID NO: 4 as Interleukin-22. However, it is noted that, while applicant may be their own lexicographer, the nucleic acid of SEQ ID NO: 3 does not encode the protein which has attained recognition in the art as being Interleukin-22. See enclosed NCBI printout of locus HSA277248, "Homo sapiens IL-22 gene for interleukin 22, exons 1a-5".

Objections and Rejections under 35 U.S.C. §§101 and 112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 74-75, 83-90, 113-117, and 122-127 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The instant application discloses a portion of a protein which applicants designate Interleukin 22 (IL-22) and a nucleic acid which encodes such, SEQ ID NO: 3. The specification states at page 11 that the cDNA was isolated from a epileptic frontal cortex cDNA library. At page 71 it is

disclosed that the nucleic acid is expressed in bone marrow, skeletal muscle, and brain. At page 11, it is clearly stated that SEQ ID NO: 3 is only a partial open reading frame, that is, that the complete coding sequence is not represented. At pages 12-13 there is a structural analysis of the putative protein, stating that it is related to IL-20 and IL-17 based on similarity in a number of small domains; however, there is no functional significance disclosed for those domains. The specification teaches at page 70 that probes to detect SEQ ID NO: 3 may be used in a variety of forensic and diagnostic methods. Other disclosed uses are in chromosome mapping, gene therapy, antisense, and tissue typing. The protein encoded thereby is stated to be useful in assays, or diagnostic or treatment methods (see page 72, for example). At page 74, it is disclosed that both IL-21 and IL-22 modulate secretion of IL-6 from NIH-3T3 cells. Because applicants claim the nucleic acid in terms of the protein it encodes, the utlity of the protein can be considered in determining utility of the nucleic acid that could be used to produce such recombinantly. There is no other specific biological activity disclosed for the protein, however, the specification contains conjecture such that the protein encoded by the claimed nucleic acid may activeate or inhibit proliferation, differentiation or mobilization of immune cells (page 75). At pages 76-81 a number of possible uses for the encoded protein are presented, including treatment of hyperproliferative disorders, infections disease, regeneration of tissue, chemotaxis, and binding. There is no working example in which any biological activity is demonstrated for the protein, nor any use is demonstrated for the claimed nucleic acid.

None of the aforementioned uses is considered to be specific, substantial and credible, as set forth in the Utility Examination Guidelines of 1/5/2001, Federal Register 66(4) beginning at page 1092. It is not predictable that IL-22 will share function with other interleukins, nor if so, what functions would be shared. The assertion that the disclosed IL-22 would have biological activities as set forth above cannot be accepted in the absence of supporting evidence, because the proposed activities of the protein or other uses of the claimed nucleic acid are merely conjectural, and the specification 'discloses' numerous mutually exclusive activities or uses, such that none can be considered to be credible without any supporting evidence. Further, the relevant literature indicates that prediction of function from structure is not accurate, and reports examples of polypeptide

families wherein individual members have distinct, and sometimes even opposite, biological activities, such that the scattered similarities to other known interleukins cannot be taken to be predictive of any particular function. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Accordingly, in view of the cited art, the skilled artisan would not accept, without experimental confirmation, that IL-22 would have any particular of the plethora of proposed activities.

With regard to the remaining uses asserted by applicants, the disclosed use for diagnosis of

chromosomal disorders is not credible, in the absence of any disclosed chromosomal disorder, or any disease or condition which could be so diagnosed. Use for chromosomal mapping is not considered by the Patent Office to be a specific or substantial utility, as such use could be asserted for *any* cDNA. Use in RFLP or forensic analysis is similarly non-specific, as such use could be asserted for *any* cDNA. It is further noted that because applicants claim the nucleic acid in terms of the protein it encodes, that only a minority of such nucleic acids would be found to be enabled, even if chrmosomal hybridization, tissue typing, anti-sense therapy or any other utility that relies upon hybridization to a naturally occuring sequence were found to constitute a sufficient utilty under 35 U.S.C. §101. No assertion of diagnostic or therapeutic use of either the claimed nucleic acids nor the protein encoded thereby can be considered to be specific or substantial, much less credible, as there is no disclosure of any condition which can be so diagnosed or treated. The disclosure that the encoded protein may modulate immune system cell proliferation and differentiation in a dose-dependent manner is merely an invitation to experiment, and would not be considered credible by one of skill in the art; mere homology and expression patterns is not accepted by those of skill in the art as being predictive of function, and the term "modulate" can encompass either a positive or negative effect. Finally, although there is a clear statement that the protein encoded by the claimed nucleic acid modulates secretion of IL-6 from NIH-3T3 cells, this does not satisfy the utility requriment because it is not clear whether this is positive or negative modulation nor under what conditions such occurs, and because it is not clear what utlity such an effect would convey. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a nucleic acid encoding a protein

which has undetermined function or biological significance, and polynucleotides encoding such. Until some actual and specific activity can be attributed to the protein identified in the specification as IL-22 protein or the polynucleotides encoding it, the claimed invention is incomplete.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 74-75, 83-90, 113-117, and 122-127 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 83 is indefinite for failing to indicate the relationship between the recited structural elements. Specifically, it is not clear how the "heterologous polynucleotide" of claim 83, for example, relates to the polynucleotide of claim 74. In claim 84, it is not clear whether applicants intend an operable attachment that would produce a fusion protein, or merely that the two recited portions be present on the same vector.

Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 113-117, 122 and 124 are rejected under 35 U.S.C. 102(b) as being anticipated by M. Bonaldo et al., locus HUMNOTIA.

Locus HUMNOTIA is 99.2% identical to bases 21-276 fo SEQ ID NO: 3. As a cDNA, it would necessarily have been double-stranded, and would inherently have been in a vector and host cell to allow propagation of the clone. Accordingly, the claims are anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:Bonaldo et al., locus HUMNOTIA

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the

contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 123 and 125-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonaldo et al., locus HUMNOTIA in view of Sibson et al., WO94/01548.

The primary reference does not specifically disclose recombinant expression of the protein encoded by the disclosed cDNA.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA's disclosed as Locus HUMNOTIA to express and then isolate the encoded polypeptide as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

WO/00/15798, Presnell et al., cited by applicants, discloses a protein designated zTGF beta-9, the coding sequence for which is 99.8% identical to bases 21-1642 of SEQ ID NO: 3.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Spector via telephone number 703-746-5228. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

LMS
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